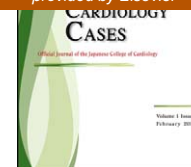




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Case Report

Recurrent intra-cardiac thrombosis—A unique presentation of prothrombin G20210 mutation

Kartika Shetty (MD)*, Nirmal Sunkara (MD), Chowdhury Ahsan (MD)

Department of Cardiology, University of Nevada School of Medicine, Las Vegas, NV, USA

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KEYWORDS

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Summary We report a 49-year-old female patient with recurrent large left ventricular thrombus on echocardiogram in an apparently normal heart and insignificant cardiac past medical history. She underwent an excision of the left ventricular mass, final biopsy on which proved it to be a thrombus. Postoperative anti-coagulation was initiated with enoxaparin and warfarin and the patient was followed up at a cardiology clinic 6 weeks later. A repeat trans-thoracic echocardiogram revealed a new mass arising from the left atrium. Considering the increased risk of repeat ventriculostomy, she was treated conservatively with her current management. During this time the patient's pro-thrombotic work-up revealed positive prothrombin G20210 mutation. A follow up trans-thoracic echocardiogram done 2 months later surprisingly revealed complete resolution of the intracardiac mass. Our patient had prothrombin G20210 mutation, an entity primarily known for deep venous thrombosis, which rarely causes intra-arterial thrombus, intra-cardiac being unreported. There are no established protocols for management of these cases. The rate of embolic episodes in mobile pedunculated thrombi is reported as high as 60%. Patients with prior embolism must be offered immediate surgery, especially if the thrombus is large with an irregular surface, pedunculated, and multiple in number. Aggressive anti-coagulation with close monitoring is essential.

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1. Case report

We present a case of a 49-year-old Hispanic female who presented to the emergency room with shortness of breath on

exertion, which had been ongoing for one month. Her past medical history was significant for anxiety and hypertension for 5 years for which she was on metoprolol. She denied taking any other medications. The patient had a history of hysterectomy. She denied smoking, alcohol abuse, or recreational drug abuse. There was no significant family history for medical illness.

She was afebrile on examination, pulse rate was 72 beats per minute, respiratory rate was 16 breaths per minute and blood pressure was 132/82 mmHg. No signs of endocarditis were noted on general exam.

* Corresponding author at: Department of Cardiology, University of Nevada School of Medicine, 2040 West Charlesaton Blvd, Suite 300, Las Vegas, Nevada 89102, USA. Tel.: +1 702 824 7687; fax: +1 702 671 2376.

E-mail address: Kartikashetty@yahoo.com (K. Shetty).

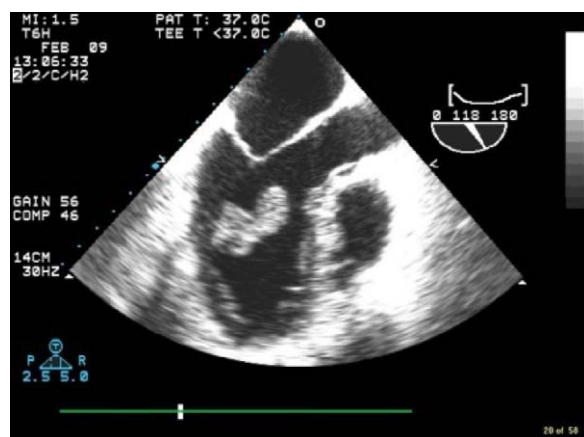


Fig. 1 Trans-esophageal echocardiogram showing a partly pedunculated thrombus in the left ventricle.

Heart auscultation did not reveal murmurs, rubs, or gallops.

Chest was clear to auscultation bilaterally.

Her complete blood count was essentially normal with a platelet count of 236,000 per mm³. Her prothrombin time was 11s and international normalized ratio (INR) was 1. Her C-reactive protein was 13mg/L. Autoimmune panel was negative. Antithrombin was 24.6mg/dL, and anti-cardiolipin, IgG, and IgM were negative. Homocysteine was 6.8 μmol/L, factor V Leiden was negative.

Patient protein C was 11 IU/dL and protein S 20 IU/dL.

On initial work-up she was found to have a left ventricular mass on echocardiogram.

A trans-esophageal echocardiogram confirmed this (Fig. 1). The patient did not have clinical signs suggestive of vascular thrombosis in other organ system.

She was afebrile and blood cultures were negative. Cardiothoracic surgery was consulted. She had an excision of the left ventricular mass and recovered from this well post-operatively. Intra-operative findings specified a large left ventricular mass affixed to the base of the left posterolateral papillary muscle at two discrete locations. Final biopsy demonstrated a thrombus (Fig. 2).

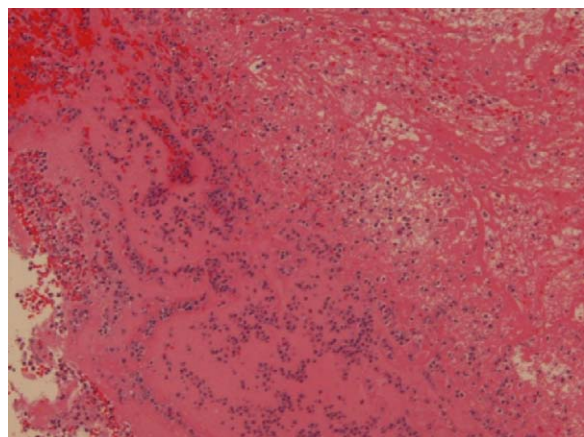


Fig. 2 A Hematoxylin & Eosin stained slide of the excised cardiac thrombus showing characteristic clumps of platelets interspersed with thrombin.

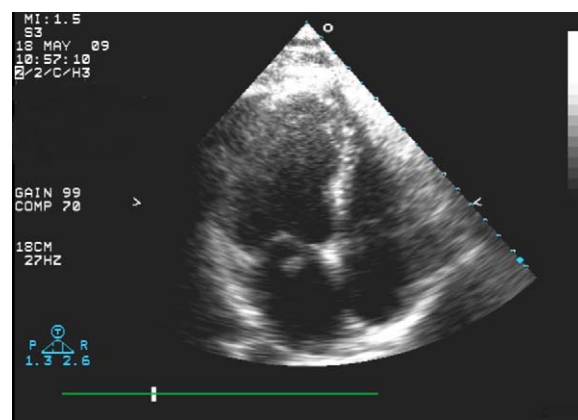


Fig. 3 Trans-thoracic view of a new pedunculated thrombus in the atrium.

Anticoagulation was initiated with enoxaparin and warfarin for first few days and later switched to warfarin only. She had been therapeutic on warfarin for the last couple of days before discharge in a stable condition.

At routine follow-up at 6 weeks, the patient had no untoward symptoms and the patient's INR was therapeutic. A repeat trans-thoracic echocardiogram was ordered which revealed a new mass arising from the left atrium (Fig. 3). This study was followed-up by a trans-esophageal echocardiogram confirming the finding (Fig. 4).

During this time period patient's pro-thrombotic work-up revealed positive prothrombin G20210 mutation.

A decision was made after consultation with cardiothoracic surgeons to conservatively treat the patient with anti-coagulation and monitor closely. This consensus was heavily influenced by risk of repeat ventriculostomy.

A follow-up trans-thoracic echocardiogram 2 months later with the patient being on anti-coagulation therapy surprisingly revealed complete resolution of the intra-cardiac mass (Fig. 5).

2. Discussion

We report a patient with a large left ventricular thrombus in an apparently normal heart and insignificant cardiac

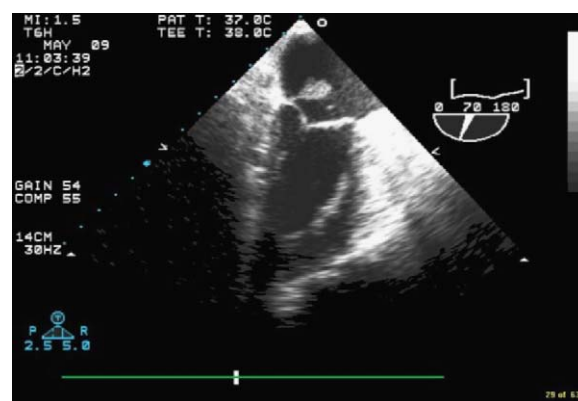


Fig. 4 Trans-esophageal echocardiographic view of left atrium with a new pedunculated thrombus.

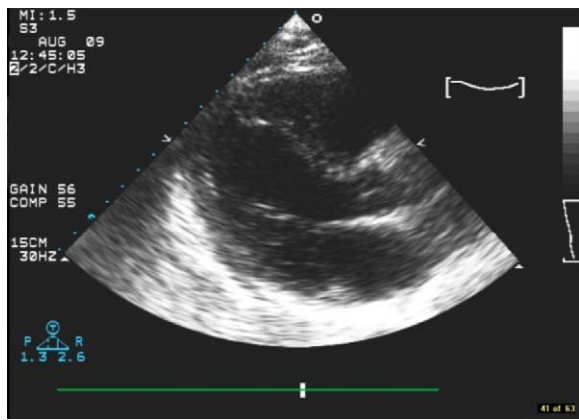


Fig. 5 A trans-thoracic echocardiogram done 6 weeks later shows complete resolution of the thrombus.

past medical history. Our patient had prothrombin G20210 mutation, which rarely causes intra-arterial thrombus, with intra-cardiac thrombus in a normal heart being even rarer [1,2]. Our literature search found a case report of right ventricular thrombus in a patient with right ventricular arrhythmogenic dysplasia with G20210 mutation [3].

This entity is mainly known for deep venous thrombosis [4,5] and accounts for a substantial number of inherited thrombophilia cases [6,7]. The influence of prothrombin gene mutation and other inherited genetic abnormalities on arterial thrombosis remains controversial. A meta-analysis of published case-control and cohort studies correlating the factor V Leiden, prothrombin G20210A, and other genetic abnormalities with myocardial infarction, ischemic stroke, or peripheral vascular disease showed modest association [8].

3. Prothrombin G20210A

Prothrombin (factor II) is the precursor of thrombin, the end-product of the coagulation cascade. It is synthesized in the liver and is post-translationally modified in a vitamin K dependent reaction that converts ten glutamic acids on prothrombin to gamma-carboxyglutamic acid. It has a half-life of 3–5 days. The human prothrombin gene spans 21 kb on chromosome 11p11-q12 and consists of 14 exons and 13 introns. A transition (guanine to adenine) at nucleotide 20210 in the 3' untranslated region of the prothrombin gene was shown as a risk factor for thrombosis [9]. Linkage analysis demonstrates that the prothrombin G20210A mutation is a functional polymorphism and it influences both plasma prothrombin levels and risk of thrombosis [9].

The proportion of the white population heterozygous for the allele varies from 0.7% to 6.5%, with the highest prevalence rates reported in Spain [10]. Heterozygous carriers have 30% higher plasma prothrombin levels than normal subjects [9].

4. Risk of thrombosis

4.1. Deep vein thrombosis

The G20210A prothrombin gene mutation has been found with greater frequency in patients with venous thrombosis than controls in a number of studies from Europe, the USA, and Brazil [7,9–12]. In the Leiden Thrombophilia Study, the 20210 allele was found in 6.3% of consecutive unselected patients with a first episode of deep vein thrombosis in comparison to 2.3% of healthy matched controls who had the prothrombin gene mutation [9] indicating that the 20210 allele is a relatively common risk factor for venous thrombosis. The study also showed the 20210 allele to be associated with elevated prothrombin levels.

However, data on the rate of recurrent deep vein thromboses remains ambiguous. Two meta-analyses have come to differing conclusions concerning whether the presence of the prothrombin gene mutation is (odds ratio 1.72; 95% CI 1.27–2.31) [13], or is not (odds ratio 1.4; 95% CI 0.90–2.0) [14], associated with an increased risk for deep vein thrombosis recurrence.

The prothrombin gene mutation is also a risk factor for cerebral venous thrombosis particularly in the presence of exposure to oral contraceptives [15].

4.2. Arterial thrombosis

As mentioned earlier the association of prothrombin gene mutation and arterial thrombosis remains controversial. Although the prothrombin gene mutation is not a risk factor for cerebrovascular ischemic disease in older patients [16] a relation to stroke in younger patients has been suggested.

In a study conducted by De Stefano et al. [17] 12.5% (9/72) of patients with ischemic stroke before reaching 50 years of age and with absence of hypertension or evident metabolic risk factors were found to be carriers of the factor II G20210 gene mutation in contrast to 2.5% in 198 controls (7.6% versus 1.2%) [17]. Similarly, a study done by Lalouschek et al. [18] in male patients with a documented stroke/transient ischemic attack before 60 years of age, the prevalence of the prothrombin gene mutation was significantly higher than in controls (6% versus 1%). No significance was observed in female subjects [18].

Modest overall association was reported between the risk for myocardial infarction and ischemic stroke, particularly among younger patients and women with prothrombin and other genetic abnormalities [8,19].

There are no established protocols for management of these cases. Though dissolution of cardiac thrombus with anticoagulant therapy is reported in the literature [1], risk of embolization is ever lurking. The rate of embolic episodes in mobile pedunculated thrombi is reported as high as 60% [20]. Patients with prior embolism must be offered immediate surgery, especially if the thrombus is large with an irregular surface, pedunculated, and multiple in numbers. Aggressive anticoagulation with close monitoring is essential.

In conclusion, although we have always considered prothrombin G20210 mutation to be associated with venous thrombosis, this case establishes the importance of elucidating prothrombin G20210 mutation as a cause of arterial

system thrombosis. The fact that this patient had recurrent thrombosis in the heart, a high pressure system, shows that patients with this condition have a strong predilection for thrombosis and the threshold for evaluation and treatment should be low. Testing for G20210 should be strongly considered in select individuals.

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